REMARKS

I. Status Summary

Claims 1-4, 6-14, 36, and 38-46 are now pending in the subject U.S. patent application. In a Final Official Action dated August 9, 2007 (hereinafter the "Final Official Action"), the United States Patent and Trademark Office (hereinafter "the Patent Office") presented the following rejections.

Claims 1-3, 6-9, and 41 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by McMahan *et al.* (1996) 236 *Anal Biochem* 101-106 (hereinafter "McMahan"). Claims 1-3, 6-9, 36, 38, 39, and 41 have also been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by the Molecular Probes Technical Literature of record (hereinafter "Molecular Probes") as evidenced by McMahan. Claims 1, 2, 4, 6-9, and 41 have also been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by Ehteshami *et al.* (1996) 9 *J Mol Recog* 733-737 (hereinafter "Ehteshami *et al.*"). Claims 1, 2, 4, 6-14, and 41 have also been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by the Ehteshami Dissertation of record (hereinafter "Ehteshami").

Claim 46 has been rejected under 35 U.S.C. § 103(a) upon the contention that the claim is unpatentable over McMahan or Molecular Probes in view of Neville *et al.* (1997) 6 *Protein Sci* 2436-2445 (hereinafter "Neville") and Nieba *et al.* (1997) 252 *Anal Biochem* 217-228 (hereinafter "Nieba"). Claim 46 has also been rejected under 35 U.S.C. § 103(a) upon the contention that the claim is unpatentable over Ehteshami *et al.* in view of Neville and Nieba. Claims 40 and 42-46 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Ehteshami in view of Neville and Nieba.

Claim 40 has been canceled without prejudice.

Claims 1, 10, 14, 36, 41, and 46 have been amended. Support for the amendments can be found throughout the specification as filed, including particularly in the Figures. Additional support can be found in the specification at page 25, lines 9-25. Accordingly, applicant respectfully submits that no new matter has been added by the amendments to the claims.

New claim 47 has been added. Support for the new claim can be found throughout the specification as filed, including particularly on page 10, line 33, through page 11, line 2. Additional support can be found on page 25, lines 13-18. Accordingly, no new matter has been added by the inclusion of the new claim.

Reconsideration of the application as amended and based on the remarks set forth herein below and the Request for Continued Examination is respectfully requested.

II. Responses to the Anticipation Rejections

Claims 1-3, 6-9, and 41 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by McMahan. Claims 1-3, 6-9, 36, 38, 39, and 41 have also been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by the Molecular Probes Technical Literature of record (hereinafter "Molecular Probes") as evidenced by McMahan. Claims 1, 2, 4, 6-9, and 41 have also been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by Ehteshami *et al.* (1996) 9 *J Mol Recog* 733-737 (hereinafter "Ehteshami *et al.*"). Claims 1, 2, 4, 6-14, and 41 have also been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by the Ehteshami Dissertation of record (hereinafter "Ehteshami").

After careful consideration of the rejections and the Patent Office's bases therefor, applicant respectfully traverses the rejections and submits the following remarks.

II.A Response to the Rejection over McMahan

Claims 1-3, 6-9, and 41 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by McMahan. According to the Patent Office, McMahan discloses a conjugate comprising a polydentate chelator and a detectable moiety conjugated to the polydentate chelator, which the Patent Office asserts appears to be identical to identical to the molecule shown in the instant specification in Figure 7. With regards to the detectable moiety, the Patent Office asserts that McMahan teaches that the detectable moiety is biotin. The Patent Office further asserts that in addition to the conjugate comprising a chelator-metal ion moiety and a detectable label, McMahan teaches that the conjugate further comprises a spacer between the chelator-metal ion moiety and the detectable label and that the conjugate is soluble in an aqueous solution. The Patent Office concedes that McMahan does not specifically teach that polydentate chelator coordinates a metal ion selected from the group consisting of Fe^{3+}, Al^{3+}, Yb^{3+}, and Ga^{3+}, but asserts that the claimed limitation does not appear to result in a manipulative difference between the claimed invention and the prior art because the specification teaches that the present invention encompasses polydentate chelators such as NTA coordinated to metal ions such as Fe^{3+}, Al^{3+}, Yb^{3+}, and Ga^{3+}.

Initially, applicant respectfully submits that claims have been amended to recite *inter alia* that the polydentate chelator is coordinated to a metal ion selected from the group consisting of Fe^{3+}, Al^{3+}, Yb^{3+}, and Ga^{3+}. Applicant respectfully submits that McMahan discloses that the metal ion chelated by the chelator is Ni^{2+}.

Therefore, applicant respectfully submits that McMahan does not teach each and every element of independent claims 1 and 41. As such, applicant respectfully submits that McMahan

does not support a rejection of claims 1 and 41 under 35 U.S.C. § 102(b). Claims 2, 3, and 6-9 all depend from claim 1, and thus are also believed to be distinguished from McMahan. Accordingly, applicant respectfully requests that the instant rejection of claims 1-3, 6-9, and 41 be withdrawn at this time.

II.B Response to the Rejection over Molecular Probes

Claims 1-3, 6-9, 36, 38, 39, and 41 have also been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by Molecular Probes as evidenced by McMahan. According to the Patent Office, Molecular Probes discloses a conjugate of the formula Biotin-X NTA comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. The Patent Office further asserts that with regards to the chelator-metal moiety, Molecular Probes teaches that the chelator is nitriloacetic acid and the metal is Ni^{2+}. The Patent Office further asserts that the reference teaches a kit comprising the conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety, and that the kit further comprises a secondary reagent for detecting the conjugate as well as instructions on how to use the kit.

Applicant respectfully submits that as with the McMahan reference, Molecular Probes teaches only reagents in which the chelated metal ion is Ni^{2+}. Given that independent claims 1, 36, and 41 of the instant application all recite that the polydentate chelator is coordinated to a metal ion selected from the group consisting of Fe^{3+}, Al^{3+}, Yb^{3+}, and Ga^{3+}, applicant respectfully submits that Molecular Probes, like McMahan, does not disclose each and every element of the instant claims.

Therefore, applicant respectfully submits that Molecular Probes does not support a rejection of claims 1, 36, and 41 under 35 U.S.C. § 102(b). Furthermore, claims 2, 3, 6-9, 38, and 39 all depend directly or indirectly from claim 1 or from claim 36, and thus are also believed to be distinguished over Molecular Probes. As such, applicant respectfully requests that the instant rejection of claims 1-3, 6-9, 36, 38, 39, and 41 under 35 U.S.C. § 102(b) over Molecular Probes as evidenced by McMahan be withdrawn at this time.

II.C Response to the Rejection over Ehteshami et al.

Claims 1, 2, 4, 6-9, and 41 have also been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by Ehteshami *et al.* According to the Patent Office, Ehteshami *et al.* teaches a conjugate at page 734, Figure 1 comprising a polydentate chelator and a detectable moiety conjugated to the polydentate chelator which appears to be identical which respect to the conjugation site as shown in the specification in Figure 7D . With regards to the polydentate chelator, the reference is asserted to teach that the chelator is iminodiacetic

acid, and with regards to the detectable moiety, the reference is asserted to teach (abstract) that the detectable moiety is biotin. In addition to the conjugate comprising a chelator-metal ion moiety and a detectable label, Ehteshami *et al.* is asserted to teach that the conjugate further comprises a PEG spacer between the chelator-metal ion moiety and the detectable label, wherein the presence of the PEG provides water solubility.

Applicant respectfully submits that Ehteshami *et al.* does not support a rejection of claims 1, 2, 4, 6-9, and 41 under 35 U.S.C. § 102(b). First, applicant respectfully submits that Ehteshami *et al.* does not teach a reagent in which a metal ion selected from the group consisting of Fe^{3+}, Al^{3+}, Yb^{3+}, and Ga^{3+} is coordinated to the chelator. Rather, the only metal ion that Ehteshami *et al.* discloses is copper. Therefore, applicant respectfully submits that Ehteshami *et al.* does not disclose each and every element of the present claims.

Additionally, applicant respectfully submits that independent claims 1 and 41 recite that the phosphoprotein detection reagent (PPDR), which comprises a polydentate chelator coordinated to a metal ion selected from the group consisting of Fe^{3+}, Al^{3+}, Yb^{3+}, and Ga^{3+}, selectively binds to a phosphorylated amino acid residue in a phosphoprotein. This selective binding occurs via a subset of the coordination sites of the metal ion. This is depicted in the instant application in Figure 2 and is also described at page 16, lines 10-13, of the instant specification. Applicant respectfully submits that the PPDRs of the presently disclosed subject matter include a metal ion for which a subset of coordination sites remains free in order to selectively bind to a target if the target is present.

Applicant respectfully submits that the reagent disclosed in Ehteshami *et al.* does not include this characteristic. As shown in Figure 1 of Ehteshami *et al.*, the metal ion coordination sites are all occupied, and an entirely different moiety of the molecule (*i.e.*, the biotin moiety) is responsible for the selective binding to targets.

Accordingly, applicant respectfully submits that there is no disclosure in Ehteshami *et al.* that includes a metal ion coordinated to a metal ion that can bind to a phosphorylated amino acid in a phosphoprotein as recited in instant claims 1 and 41. Applicant thus respectfully submits that Ehteshami *et al.* does not support a rejection under 35 U.S.C. § 102(b) of claims 1 and 41. Claims 2, 4, and 6-9 all depend from claim 1, and thus are also believed to be distinguished over Ehteshami *et al.* Applicant respectfully requests that the instant rejection of claims 1, 2, 4, 6-9, and 41 over Ehteshami *et al.* be withdrawn at this time.

II.D Response to the Rejection over Ehteshami

Claims 1, 2, 4, 6-14, and 41 have also been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by the Ehteshami Dissertation of record (hereinafter

"Ehteshami"). According to the Patent Office, Ehteshami discloses a conjugate comprising a polydentate chelator moiety and a detectable moiety conjugated to the polydentate chelator moiety via a PEG spacer group. The Patent Office further asserts that the reference teaches that the chelator is iminodiacetic acid (IDA) and that the detectable moiety is biotin.

Applicant respectfully submits that Ehteshami does not disclose any embodiments in which the chelated metal ion is Fe^{3+}, Al^{3+}, Yb^{3+}, or Ga^{3+}. As such, applicant respectfully submits that Ehteshami does not support a rejection under 35 U.S.C. § 102(b) of independent claims 1, 10, and 41.

Accordingly, applicant respectfully submits that claims 1, 10, and 41 have been distinguished over Ehteshami. Applicant further respectfully submits that claims 2, 4, 6-9, and 11-14 all depend directly or indirectly from claim 1 or claim 10, and thus are also believed to be distinguished over Ehteshami. As such, applicant respectfully requests that the instant rejection of claims 1, 2, 4, 6-14, and 41 under 35 U.S.C. § 102(b) be withdrawn at this time.

III. Responses to the Obviousness Rejections

Claim 46 has been rejected under 35 U.S.C. § 103(a) upon the contention that the claim is unpatentable over McMahan or Molecular Probes in view of Neville and Nieba. Claim 46 has also been rejected under 35 U.S.C. § 103(a) upon the contention that the claim is unpatentable over Ehteshami *et al.* in view of Neville and Nieba. Claims 40 and 42-46 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Ehteshami in view of Neville and Nieba.

After careful consideration of the rejections and the Patent Office's bases therefore, applicant respectfully traverses the rejections and submit the following remarks.

III.A. Response to the Rejections of Claim 46

Claim 46 has been rejected over McMahan or Molecular Probes in view of Neville and Nieba, and has also been rejected over Ehteshami *et al.* in view of Neville and Nieba. According to the Patent Office, Neville and Nieba cure the deficiencies of McMahan, Molecular Probes, and Ehteshami *et al.* with respect to the chelated metal ion. The Patent Office asserts that Nieba teaches that while typically the metals Ni^{2+}, Zn^{2+}, Co^{2+}, and Cu^{2+} are chelated to NTA, the choice of the metal ion for IMAC is optimized for the highest selectivity relative to other proteins not carrying the His tag.

The Patent Office further asserts that Neville teaches that Fe^{3+}-loaded NTA metal-ion affinity resin preferentially binds to phosphopeptides as compared to His-containing peptides. From this, the Patent Office asserts that it would have been *prima facie* obvious to one of skill in

the art at the time the invention was made to substitute metal ion such as Ga^{3+} or Fe^{3+} as taught by Neville in view of Nieba into the conjugates taught by McMahan, Molecular Probes, or Ehteshami *et al.* The Patent Office contends that one would have been motivated to do so because Nieba teaches that the choice of the metal ion for IMAC is optimized for the highest selectivity relative to other proteins not carrying the His tag. Additionally, Neville is asserted to teach that Fe^{3+}-loaded NTA and IDA metal-ion affinity resins preferentially bind to phosphoproteins as compared to His-containing peptides. Thus, the Patent Office asserts that one of ordinary skill in the art would have a reasonable expectation of success that by substituting the metal ion as taught by McMahan, Molecular Probes, or Ehteshami *et al.* in view of Nieba, one would achieve a metal chelate which recognizes other proteins which do not contain a His tag.

Turning first to the rejection over the combination of Ehteshami *et al.* in view of Neville and Nieba, applicant respectfully submits that the Patent Office has misinterpreted the disclosure of Ehteshami *et al.* For example, applicant respectfully submits that the Patent Office's assertion that the Abstract of Ehteshami *et al.* teaches that biotin is a detectable label is inaccurate. Rather, applicant respectfully submits that biotin is used in Ehteshami *et al.* as an affinity ligand, not as a detectable moiety.

Furthermore, applicant respectfully submits that the affinity matrix disclosed in Ehteshami *et al.* is structurally different from the reagents of the presently disclosed subject matter. As depicted in Figure 1 of Ehteshami *et al.*, the affinity matrix includes an affinity ligand (biotin) attached to a chelator via a PEG spacer. This affinity matrix is then attached to a solid support. The solid support includes the IMAC adsorbent DPA-Novarose to which a metal ion is chelated. As shown in Figures 1(A) and 1(C) of Ehteshami *et al.*, the IDA-PEG-biotin moiety is conjugated to the DPA-Novarose-Metal ion by a further chelation of the metal ion to the IDA moiety.

Therefore, applicant respectfully submits that the metal ion in Ehteshami *et al.* is chelated to DPA-Novarose on the one hand, and IDA-PEG-biotin on the other. As such, applicant respectfully submits that the metal ion is not available to act as a specific binding entity to any target of interest. In the structure disclosed in Ehteshami *et al.*, the metal ion is never chelated to anything other than IDA-PEG-biotin and/or DPA-Novarose.

This is in contrast to the structure of the presently disclosed compositions, in which one or more coordination sites of the metal ion are available to specific binding to a target of interest (*i.e.*, a phosphorylated amino acid), if present. Applicant therefore respectfully submits that the composition disclosed in Ehteshami *et al.* and the presently disclosed compositions have

different structures that perform different functions.

Summarily, applicant respectfully submits that the Patent Office has not considered the cited references in their entireties and in context, and thus the instant rejection of claim 46 over of Ehteshami *et al.* in view of Neville and Nieba is based on inaccurate assertions with respect to these references. Applicant further respectfully submits that contrary to the Patent Office's assertion, when Ehteshami *et al.*, Neville, and Nieba are considered properly and in context, they provide no motivation for one of ordinary skill in the art to replace Cu(II) with Fe(III), and further provide no reasonable expectation that doing so would result in a metal chelate that recognizes poly-His peptides such as hemoglobin. Additionally, the provide no motivation for one of ordinary skill in the art to prepare a composition comprising (a) a metal ion selected from the group consisting of Fe^{3+}, Al^{3+}, Yb^{3+}, and Ga^{3+}; (b) a phosphoprotein detection reagent (PPDR) comprising a chelator and a detectable moiety, wherein (i) the detectable moiety is conjugated to the chelator at a site other than a potential metal ion coordination site; (ii) the chelator comprises a polydentate chelator coordinated to the metal ion to form a chelator-metal ion moiety; (iii) the chelator-metal ion moiety selectively binds to a phosphorylated amino acid residue in a phosphoprotein if present to create a chelator-metal ion-phosphoprotein (CMPP) complex; and (iv) the detectable moiety allows the CMPP complex to be detected if present; and (c) a binding solution having a pH ranging from about 5.0 to about 7.0, wherein the chelated metal ion selectively binds to the phosphorylated amino acid reside in the phosphoprotein, if present, in the binding solution as recited in claim 46.

Accordingly, applicant respectfully requests that the instant rejection of claim 46 over the combination of Ehteshami *et al.*, Neville, and Nieba be withdrawn at this time.

Turning now to the rejection of claim 46 over McMahan or Molecular Probes in view of Neville and Nieba, applicant respectfully submits that the Patent Office has apparently misconstrued the nature of the Nieba reference in its apparent assertion that Nieba teaches generally that the metal ion can be optimized to generate conjugates that bind to proteins that do not carry the His tag. In actuality, applicant respectfully submits that Nieba at best discloses that in the context of a conjugate that binds to poly-His, the metal ion can be optimized to reduce non-specific binding to proteins that do not include a poly-His.

To elaborate, the Patent Office asserts that it would have been *prima facie* obvious to substitute Ga^{3+} or Fe^{3+} as taught be Neville in view of Nieba, and further that one of ordinary skill in the art would have been motivated to do so because Nieba teaches "the choice of the metal ion for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag" (*see* Official Action at page 11). Applicant respectfully submits that this assertion

appears to indicate that the Patent Office has interpreted Nieba to suggest that different metal ions could be employed to optimize binding of the conjugates to proteins that do not carry His tags.

Applicant respectfully submits that Nieba includes no such disclosure. Rather, applicant respectfully submits that the entire disclosure of Nieba relates to IMAC binding to His-tagged proteins. For example, the only reference to employing different metal ions occurs in the Introduction of Nieba, which states in part:

> Typically Ni^{2+}, Zn^{2+}, Co^{2+}, and Cu^{2+} chelated to IDA or NTA have been used in chromatographic media for immobilized metal affinity chromatography (IMAC). The choice of the metal ion and buffer conditions for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag, which does not necessarily give the tightest binding of the His tag.

Nieba at page 217. Applicant respectfully submits that what is being discussed in this passage from Nieba is the selection among different metal ions in order to reduce non-specific binding of a reagent that binds to His-tagged polypeptides to polypeptides that do not have the His tag. Stated another way, applicant respectfully submits that Nieba only discloses that metal ions can chosen which reduce non-specific, background binding while maintaining an acceptable level of specific binding to a His tag. There is nothing in Nieba that suggests that any other metal ion can be employed for binding to any ligand other than a His tag.

Furthermore, applicant respectfully submits that the Patent Office's assertion that one of ordinary skill in the art would have a reasonable expectation of success that by substituting the metal ion as taught by McMahan or Molecular Probes in view of Nieba, one would achieve a metal chelate which recognizes other proteins which do not contain a His tag" (emphasis added) is also based on this same misinterpretation of Nieba. Applicant respectfully submits that Nieba cannot be read to suggest that a change in metal ion would lead to a chelate that specifically binds to non-His tagged proteins.

And finally, applicant respectfully submits that the combination of McMahan or Molecular Probes in view of Nieba also fails to suggest providing the reagent in a binding solution having a pH raging from about 5.0 to about 7.0. Particularly, applicant respectfully submits that Neville is the only reference that teaches an Fe^{3+} conjugate, and this reference teaches that the conditions for binding are with a pH of less than 3.5 (*i.e.*, 0.1 M acetic acid; *see* Neville at page 2443, second column, second full paragraph). As disclosed in Neville, binding is at pH less than 3.5 and washes are also performed with a solution of 0.1 M acetic acid, which has a pH of less than 3.5.

Applicant respectfully submits that since Neville clearly discloses the binding reagent in

a pH lower than 3.5, there would be no motivation for preparing the instantly claimed PPDR compositions in a binding solution having a pH of about 5.0 to 7.0. Therefore, for this additional reason, applicant respectfully submits that the combination of McMahan or Molecular Probes in view of Nieba fails to support the instant rejection of claim 46.

Accordingly, applicant respectfully submits that the Patent Office has not established a *prima facie* case of obviousness of claim 46 over the combination of McMahan, Molecular Probes, or Ehteshami *et al.* in view of Nieba and Neville. Applicant thus requests that the rejections of claim 46 under 35 U.S.C. § 103(a) over McMahan, Molecular Probes, or Ehteshami *et al.* in view of Nieba and Neville be withdrawn at this time.

III.B. Response to the Rejection of Claims 40 and 42-46

Claims 40 and 42-46 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Ehteshami in view of Neville and Nieba. According to the Patent Office, it would have been *prima facie* obvious to optimize the metal taught by Etheshami for Fe^{3+} in view of the teachings of Nieba and Neville. The Patent Office asserts that one of ordinary skill in the art would have been motivated to do so because each of the metal ions have been individually taught in the prior art to be successful at binding poly-His peptides. Thus, one of ordinary skill in the art would have a reasonable expectation that by substituting Cu(II) as taught by Etheshami for Fe^{3+} in view of the teachings of Nieba and Neville, one would achieve a metal chelate which recognizes poly-His peptides such as hemoglobin.

Applicant respectfully disagrees. Initially, applicant respectfully submits that none of the cited references teaches that Fe^{3+} can be used for binding poly-His peptides. As such, the Patent Office's assertion that each of the metal ions have been individually taught in the prior art to be successful at binding poly-His peptides is believed to be inaccurate.

Furthermore, applicant respectfully submits that the misinterpretation of Nieba discussed hereinabove also impacts the instant rejection. Particularly, applicant respectfully submits that contrary to the Patent Office's assertion, since Nieba does not teach or suggest that metal ion optimization can be employed to generate new specific binding activities, it provides no motivation for one of ordinary skill in the art to switch Cu^{2+} for Fe^{3+} to achieve a metal chelate that recognizes poly-His peptides such as hemoglobin.

Additionally, applicant respectfully submits that the Patent Office's reference to the page 126 of Ehteshami does not support the instant rejection.

To elaborate, applicant respectfully submits that page 126 of Ehteshami discloses the following:

> the specificity of the bioligand moiety of these biopolymers (biotin, and PAB) were tested by adding them to two-phase systems, without charging the chelate side with metal ions. Similarly, and in order to characterize the pseudo-affinity chelating effect, experiments were performed by charging it with metal ions first and then added to the two-phase systems, containing the protein, hemoglobin, rich in surface histidine (20 histidines) which has affinity for chelated metal-ions, but having no affinity for PAB or biotin.

Ehteshami at page 126 (emphases added). Applicant respectfully submits that this passage clearly indicates that the charged chelates were employed for testing for pseudo-affinity chelating, which refers to background, non-specific partitioning that results not from a desirable, specific interaction of a target with a bioligand (*i.e.*, biotin or PAB), but from an undesirable, non-specific interaction of the metal ion with, for example, surface histidines.

Therefore, applicant respectfully submits that the experiments that are described on page 126 of Ehteshami are experiments designed to assess background, non-specific binding that is attributable not to the desired interaction between the bioligand and its binding partner, but to the interaction of surface histidines on non-target proteins with the metal ion. Applicant respectfully submits that this is clear from the juxtaposition of the two conditions presented on page 126: either the chelate is not charged, resulting in 100% of the partitioning observed being due to the specific interaction of the bioligand with its target, or the chelate is charged and the partitioning observed is due to the combination of the specific interaction of the bioligand with its target and the non-specific interaction of the metal ion with surface histidines that may be present in proteins generally. Since characterization of the interaction that is desirable will be compromised by the non-specific interaction with metal ions, the investigator wished to determine to what extent the non-specific interaction would occur.

As such, applicant respectfully submits that the disclosure of Ehteshami cannot be read to suggest that there is a desirable, specific interaction between the chelated metal ion and a target protein. This is in marked contrast to the nature of the presently claimed reagents, for which the desirable, specific interaction is between the target proteins and the chelated metal ion. In fact, applicant respectfully submits that page 132 of Ehteshami explicitly states that "as it can be seen from Table 5.1-2, the presence of the metal ions in bioligands-PEG-IDA-CU(II) has no significant effect on partitioning of avidin (emphasis added).

Therefore, applicant respectfully submits that contrary to the Patent Office's assertion on page 16 of the Final Official Action, Ehteshami read in context and in its entirety does not suggest that any embodiments disclosed therein employ the metal ion to specifically bind any target. Therefore, applicant respectfully submits that one of ordinary skill in the art upon

consideration of Ehteshami would have had no motivation to "optimize" the metal taught by Ehteshami because the metal ion employed, Cu^{2+}, functioned exactly as desired: it had "no significant effect on partitioning of avidin", which means it caused no increase in background.

Furthermore, applicant respectfully submits that the Patent Office's assertion that one of ordinary skill in the art would have been motivated to substitute the Cu(II) of Ehteshami for Fe(III) in view of the teachings of Nieba and Neville "because each of the metal ions have been individually taught in the prior art to be successful at binding poly-his peptides" is inaccurate. Applicant respectfully submits that the Patent Office has provided no references that teach that chelated Fe^{3+} binds to poly-his peptides. In fact, applicant respectfully submits that the only reference that discusses Fe^{3+} is Neville, and this reference does not teach that Fe^{3+} can be used to bind to poly-his. Rather, applicant respectfully submits that Neville teaches that incomplete loading of the chelator with Fe^{3+} can result in binding to His-containing peptides (*see* Neville at page 2437). Therefore, applicant respectfully submits that one of ordinary skill in the art would understand Neville to disclose that when Fe^{3+} is loaded properly and completely into a chelator, binding to His-containing peptides does not occur.

Additionally, applicant respectfully submits that the combination of Ehteshami in view of Neville and Nieba does not support an obviousness rejection of a composition comprising a binding solution having a pH ranging from about 5.0 to about 7.0 as presently claimed. At best, the cited combination might be asserted to teach employing an Fe^{3+} chelated reagent in the binding of the reagent to a target at less than pH 3.5. Thus, applicant respectfully submits that one of ordinary skill in the art would have had no motivation to provide the composition of claims 40 and 42-46.

And finally, applicant respectfully submits that the Patent Office has not cited any reference that teaches or suggests that Ga^{3+} could be employed as the metal ion in a chelator for phosphoprotein detection as recited in claim 42. Therefore, with respect to claim 42, this claim is also believed to be distinguished over the cited combination.

Accordingly, applicant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claims 40 and 42-46 over the combination of Ehteshami in view of of Nieba and Neville. Claim 40 has been canceled, and thus the instant rejection is believed to be moot as to this claim. As such, applicant respectfully requests that the instant rejection of claims 42-46 be withdrawn, and further that the claims be allowed at this time.

IV. Discussion of the New Claim

New claim 47 has been added. Support for the new claim can be found throughout the

specification as filed, including particularly on page 10, line 33, through page 11, line 2. Additional support can be found on page 25, lines 13-18. Accordingly, no new matter has been added by the inclusion of the new claim.

Claim 47 is believed to be distinguished over the art of record for the reasons set forth hereinabove with respect to claim 36, the claim from which it depends. Particularly, applicant respectfully submits that claim 47 recites *inter alia*

CONCLUSIONS

In accordance with the amendments to the claims and the remarks presented hereinabove, applicant respectfully submits that claims 1-4, 6-14, 36, and 38-46 are in condition for allowance, and respectfully solicits a Notice of Allowance to that effect.

Should there be any minor issues outstanding in this matter, Examiner Fetterolf is respectfully requested to telephone the undersigned attorney. Early passage of the subject application to issue is earnestly solicited.

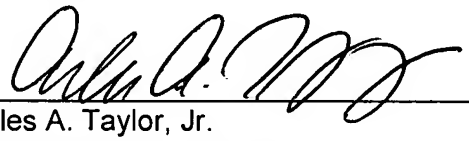
Deposit Account

The Commissioner is hereby authorized to charge any deficiency in payment or credit any overpayment associated with the filing of this correspondence to Deposit Account Number **50-0426**.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: October 31, 2007

By: 

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